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09/787,986	06/27/2001	Richard James Lewis	14438	1227

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EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1653	20

DATE MAILED: 09/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/787,986	LEWIS ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *11-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 16-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 1-34 are pending.

Applicants' amendment filed on June 13, 2003 (Paper No. 19) is acknowledged, and applicants' response has been fully considered. Claims 3, 5, 16, 17, 22 and 24-27 have been amended, and new claims 28-34 have been added. Claims 11-15 are non-elected inventions, thus withdrawn from consideration. Therefore, claims 1-10 and 16-34 are examined.

Rejection Withdrawn

Claim Rejections - 35 USC § 101 and 112

2. The previous rejection of claims 24 and 25, under 35 U.S.C.101, is withdrawn in view of applicants' amendment to the claim and applicants' response at page 7 in Paper No. 19. The previous rejection of claims 24 and 25, under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicants' amendment to the claim and applicants' response at pages 7 and 15 in Paper No. 19.

Claim Objection

3. Claim 3 is objected to because of the use of "SEQ ID NO. 1" and "SEQ ID NO. 2". Use of "SEQ ID NO: 1" and "SEQ ID NO: 2" is suggested. Claim 3 is also objected to because the claim recites "O" in the sequence, but does not indicate what "O" is. Applicants indicate the specification describes "O" being "4-hydroxyproline", which should be cited in the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-3, 5-10 and 16-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for two χ-conotoxin peptides, χ-MrIA (SEQ ID NO:1) and χ-MrIB (SEQ ID NO:2) having the ability to inhibit a neuronal amine transporter; or a composition comprising χ-MrIA or χ-MrIB, does not reasonably provide enablement for a χ-conotoxin peptide or a modified χ-MrIA or χ-MrIB having the ability to inhibit a neuronal amine transporter, wherein the amino acid sequence of the χ-conotoxin peptide is not defined; a chimeric peptide comprising the χ-conotoxin peptide and a biologically active peptide; a composition comprising the χ-conotoxin peptide; a method for treatment or prophylaxis of urinary or cardiovascular diseases, mood disorders, pain, inflammation or a disease by administering the χ-conotoxin peptide, where the disease is not defined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-3, 5-10 and 16-34 encompass a χ-conotoxin peptide or a modified χ-MrIA or χ-MrIB having the ability to inhibit a neuronal amine transporter (claims 1-3, 5-10); a chimeric peptide comprising a χ-conotoxin peptide and a biologically active peptide (claim 16); a composition comprising a χ-conotoxin peptide (claims 22 and 23); or a method for treatment or prophylaxis of urinary or cardiovascular diseases, mood disorders, pain, inflammation or a

disease by administering a χ-conotoxin peptide (claims 17-21 and 24-34). The specification, however, only discloses cursory conclusions (page 1, lines 3-9; page 1, line 29-page 2, line 1) without data supporting the findings, which state that novel χ-conotoxin peptides and derivatives are useful as inhibitors of neuronal amine transporters of neurotransmitters such as noradrenaline and in the prophylaxis or treatment of conditions such as incontinence, cardiovascular conditions and mood disorders. There are no indicia that the present application enables the full scope in view of χ-conotoxin peptides and a method of treating urinary or cardiovascular diseases, mood disorders, pain or inflammation as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the presence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding χ-conotoxin peptides, chimeric peptides containing χ-conotoxin peptides and the treating conditions for various diseases, which are not adequately described or demonstrated in the specification.

(2). The presence or absence of working examples:

The specification indicates the sequences of two χ-conotoxin peptides, χ-MrIA and χ-MrIB and demonstrates χ-MrIA has the ability to inhibit a neuronal noradrenaline transporter. However, there are no working examples indicating the claimed methods in association with claimed variants.

(3). The state of the prior art and relative skill of those in the art:

The prior art (e.g., U. S. Patent 5,441,985; WO 98/22126; Ardid et al., Fundam. Clin. Pharmacol. 6, 75-82 (1992)) indicates a method of treating lower urinary tract disorder employing an aryloxypropylamine which inhibits noradrenaline (norepinephrine) uptake and has negligible anticholinergic effect; use of an acetylcholine receptor antagonist such as α-conotoxin ImI and MII as a cardiovascular agent; or use of noradrenaline uptake inhibitors such as desipramine for the treatment of chronic pain. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identities of various χ-conotoxin peptides, the treating conditions for various diseases such as urinary or cardiovascular diseases, mood disorders, pain or inflammation, and the effects of various χ-conotoxin peptides in the treatment.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to various χ-conotoxin peptides having the ability to inhibit a neuronal amine transporter; a chimeric peptide comprising the χ-conotoxin peptide and a biologically active peptide; a composition comprising the χ-conotoxin peptide; or a method for treatment or prophylaxis of urinary or cardiovascular diseases, mood disorders, pain or inflammation, or an undefined disease by administering a χ-conotoxin peptide. The specification

only indicates the amino acid sequences of two χ-conotoxin peptides, χ-MrIA and χ-MrIB (page 3, lines 5-15), cites various possible modifications for derivatives of χ-conotoxin peptides (pages 4-11), and shows χ-MrIA has the ability to inhibit a neuronal noradrenaline transporter but negligible activity as an anticholinergic agent, a sodium channel blocker or an inhibitor of dopamine transporter (Examples 1-6). However, the specification does not identify any derivatives of χ-MrIA or χ-MrIB, nor demonstrates any χ-conotoxin peptide other than χ-MrIA having the ability to inhibit a neuronal amine transporter. The specification has not demonstrated the use of any χ-conotoxin peptide for treating various diseases such as urinary or cardiovascular diseases, mood disorders, pain or inflammation. There are no working examples indicating the claimed methods in association with claimed variants. The specification fails to provide the treating conditions such as the dose and the time for various diseases cited, nor the effect of the χ-conotoxin peptide in the treatment. Since the specification fails to provide sufficient teachings on the identities of various χ-conotoxin peptides and the treating conditions for various cited diseases, it is necessary to have additional guidance on the use of χ-conotoxin peptides and to carry out further experimentation to assess the effects of these χ-conotoxin peptides in the treatment of various diseases.

(5). Predictability or unpredictability of the art:

The specification indicates χ-MrIA has the ability to inhibit a neuronal noradrenaline transporter (Example 1), and cites the prior art (U. S. Patent 5,441,985) shows compounds which inhibits noradrenaline uptake and has negligible anticholinergic effect are useful for treating lower urinary tract disorder (page 2, lines 3-9). However, the compounds cited in the art are small organic molecules, which are structurally different from χ-conotoxin peptides.

Furthermore, the specification does not demonstrate the treating conditions for various diseases using a χ-conotoxin nor the effect of the χ-conotoxin in the treatment. Since various χ-conotoxin peptides are not identified, and the treating conditions for various diseases using the χ-conotoxin peptides are not sufficiently described, the outcome of the claimed method is highly unpredictable.

(6). Nature of the Invention

The scope of the claim includes various χ-conotoxin peptides and using χ-conotoxin peptides in treating various diseases such as urinary or cardiovascular diseases, mood disorders, pain or inflammation, or an undefined disease, however the specification has not demonstrated the treatment of these pathological conditions using an identified χ-conotoxin peptide. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, and the teachings in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of various χ-conotoxin peptides in treating various diseases.

In response, applicants indicate χ-conotoxin peptides are a new class of conotoxin peptides which inhibit neuronal amine transporters, once the activity of a class of conotoxin peptides has been determined, it is possible to use assays as exemplified in Example 5 to identify other conotoxin peptides of the same class in venoms; there are nine additional χ-conotoxin peptides other than χ-MrIA or χ-MrIB being tested; small molecules and peptides have many features in common, including stability and biological activity, thus results associated with small molecules with a particular mode of action, e.g., noradrenaline transporter inhibition, can be

extrapolated directly to peptides with the same essential pharmacology, therefore small molecule inhibitors of noradrenaline reuptake have the same type of effects in vivo as their peptide counterparts, and the specification provides examples showing inhibitors of noradrenaline reuptake have therapeutic use in the treatment of cited diseases; the specification have provided teachings, guidance and working examples, a skilled person can make other χ-conotoxins and use the claimed variants for the treatment of cited diseases without undue experimentation; Exhibit A indicates MrIA produced the same dose-dependent antinociceptive effect as morphine in a rat model; and 35 U.S.C. 112 does not require inventors provide examples and conditions for every use of the claimed invention (pages 8-14 of the response). The response has been fully considered, however, the argument is not found persuasive because of the following reasons: The function of a compound depends on its structure, in order to identify other χ-conotoxin peptides in venoms, it is not only required to test the activity of the peptide using the assays of Example 5, it is also necessary to carry out further experimentation to identify its amino acid sequence as a χ-conotoxin peptide. Although nine sequences of χ-conotoxin derivatives are listed at page 10 of the response, there are no data indicating their activities of inhibiting noradrenaline transporter and their use in the treatment of various cited diseases, thus further experimentation is also needed about their effects in the treatment. Regarding extrapolating the in vivo data of small molecule which has the same activity of inhibiting noradrenaline transporter to the in vivo effect of χ-conotoxin peptide, since the specification does not teach how to extrapolate the in vivo effect of small molecule to χ-conotoxin peptide and there are no structural similarity between the two types of compounds, it is necessary to carry out further experimentation to confirm the in vivo effect of χ-conotoxin peptide. Regarding the data shown

in Exhibit A, Fig. 1 only indicates MrIA has some antinocicepticve effect in a rat model of neuropathic pain, however, the data on morphine and saline (the control) are not shown, thus, it is not clear how much effect MrIA has in the treatment of neuropathic pain in animal model. Regarding the examples and conditions for use of the claimed invention, since the specification does not show any example for in vivo treatment of various cited diseases, nor has provided sufficient teachings on how to extrapolate the in vivo effect from small molecules to χ-conotoxin peptides, the identities of various χ-conotoxin peptides and the effects of various χ-conotoxin peptides as indicated in the section above, while the claims encompass unspecified variants and methods of treating various diseases associated with variants, thus it is necessary to carry out further experimentation to assess the effects of various χ-conotoxin peptides in the treatment of various diseases.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 3, 4, 16-21 and 24-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 3 and 4 are indefinite because of the use of the term "one or more amino acid deletion, additions, substitutions or side chain modifications". The term "one or more amino acid deletion, additions, substitutions or side chain modifications" renders the claim indefinite, it is unclear which amino acids are deleted, added, substituted or modified at side chains, and what amino acid sequences are obtained after modification. Claim 4 is also indefinite because the

claim recites "χ-MrIA" and "χ-MrIB" without indicating sequence identifier, it is not clear which χ-conotoxin is "SEQ ID NO: 1", and which χ-conotoxin is "SEQ ID NO: 2". Claim 4 is included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which it depends.

In response, applicants indicate the specification teaches peptides can tolerate significant changes while still retaining activity, claim 3 includes a functional recitation, and specification provides assays for testing activity and methods of guiding amino acid modification (pages 13-14 of the response). The response has been fully considered, however, the argument is not found persuasive because the claim does not recite a defined structure for the modified peptide, even though a functional language is cited in the claim, it is not clear what amino acid sequence is functional.

7. Claim 16 is indefinite because of the use of the term "a chimeric peptide comprising a segment or a sequence of a naturally occurring χ-conotoxin peptide and a segment or sequence of another biologically active peptide or protein, and wherein said chimeric χ-conotoxin peptide possesses .....and an activity associated with said other peptide or protein". The cited term renders the claim indefinite, it is unclear which biologically active peptide or protein is intended, which segment of the χ-conotoxin peptide or the other peptide is used for the chimeric peptide, and which activity the other peptide possesses.

In response, applicants indicate claim 16 has been amended (page 14 of the response). The response has been fully considered, however, the argument is not found persuasive because the amended claim does not resolve the issue of indefiniteness as indicated in the paragraph above.

8. Claims 17-21 and 24-34 are indefinite because the claims lack essential steps in the method of treating diseases such as urinary, cardiovascular diseases, mood disorder, pain and inflammation. The omitted step is the outcome of the treatment. Claims 18-21, 25-29 and 31-34are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

In response, applicants indicate the claim includes the step of administration of a χ-conotoxin; the method of administration is not required in a treatment claim; the recitation of "treatment" indicates the outcome, e.g., the pathological condition is inhibited, reduced or eliminated; and claim 17 has been amended to recite the administration routes to expedite favorable prosecution (page 14 of the response). The response has been considered, however, the argument is not fully persuasive because the recitation of "treatment" only indicates the disease is treated with a χ-conotoxin, it does not indicate the treatment is effective and has a desired outcome such as the pathological condition is inhibited, reduced or eliminated, thus, the claimed method does not have endpoint in the treatment. Regarding the method of administration, the argument is persuasive, thus rejection is withdrawn.

9. Claim 24, 25, 30 and 32 are indefinite because of the use of the term "diseases and conditions". The term "diseases and conditions" renders the claim indefinite, it is unclear what diseases and conditions are intended.

In response, applicants indicate claims 24-27 have been amended and claims 28-34 have been added to indicate what the diseases and conditions are (page 15 of the response). The response has been fully considered, however, the argument is not found persuasive because claims 24, 25, 30 and 32 still recite this term without identifying what they are.

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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August 29, 2003

Christopher S. F. Low
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